REMARKS

After entry of this amendment, the claims pending are claims 1, 2, 4-10 and 12-15. Any subject matter canceled from the claims by amendment is reserved for refiling in a continuation application filed during the pendency of this application. Applicants further affirm the correctness of the inventive entity in view of the cancellation of claims.

Claim 1 is amended to clarify the subject matter of the invention. Support for these amendments is found in the specification and particularly on pages 99-102. No new matter is introduced by this amendment.

Rejections Under 35 USC §103(a)

> Claims 1, 2, 4-10 and 12-15 are rejected under 35 USC §103(a) as being unpatentable over Liu *et al*, **1999** *Arterio. Thromb. Vasc. Biol.,19*:2207-2213 ("Liu") or D. Drayna *et al*, **1987** *Nature, 327*:632-634 ("Drayna"), in view of US Patent No. 5,955,443 ("Bennett").
>
> The examiner contends that it would be obvious to make and use antisense oligos targeting certain regions of human cholesteryl transfer protein (CETP) because Drayna refers to CETP as playing a role in pathological homeostasis; Liu refers to an antisense compound to CETP and teaches that inhibiting CETP may counteract atherosclerosis; and Bennett refers to modifications to antisense compounds. The examiner further states that a reasonable expectation of success of making said oligos is derived from Liu's demonstration of use of a single oligo and Bennett's demonstrates of how to modify oligos.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

A. The combination of Drayna and Bennett does not make obvious the present invention.

Drayna is a 16-year old reference that teaches the cloning and sequencing of a human CETP DNA. The limited teaching as to the use of CETP resides in a mere suggestion that

> "The transfer of insoluble cholesteryl esters among lipoprotein particles is a vital step in normal cholesterol homeostasis and ***may be involved*** in the development of atherosclerosis". (Emphasis added, page 632, col. 1).

Drayna further states that the CETP reaction is the *least characterized* of the catalyzed steps of the cholesterol transport pathway. Drayna concludes the analysis of the characteristics (e.g., hydropathicity, tissue distribution, etc.) of the protein and its mRNA with the acknowledgement:

> "***Future experiments*** with hybridization of CETP probes to RNA extracted from tissues and *in situ*, and with the transfer protein purified from cell cultures expressing the cloned gene, ***should help to elucidate*** *activities* of CETP in normal and in pathological cholesterol homeostasis." (Emphasis added; page 634, the sentence spanning cols. 1 and 2).

Thus, Drayna teaches nothing about CETP other than *suggestions* for *possible* biological activities. Drayna, alone or in combination, does not teach or suggest antisense compounds. Drayna does not teach or suggest any sequences within CETP for successful hybridization of any antisense compounds, such that an inhibitory activity of CETP is demonstrated.

Drayna does not teach or suggest anything in combination with Bennett that would make obvious the subject matter of the pending claims of this invention.

Bennett refers to antisense compounds that modulute a completely unrelated protein to CETP, namely platelet endothelial cell adhesion molecule-1 (PECAM-1). Bennett contains no disclosure that suggests or refers to the protein CETP. Without any disclosure of CETP, Bennett cannot provide any suggestion which permits one to identify or suggest specific CETP sequences as target sequences for binding by an antisense sequence. Bennett does not teach or suggest any sequence for antisense compounds that bind to CETP, as required by claim 1. Nor does Bennett suggest any methods for using the sequences of claim 1. Bennett does not teach or suggest a therapeutic utility of antisense compounds that bind CETP.

Bennett, no more than Drayna, is able to teach or suggest the particularly recited CETP sequences as targets for Applicant's oligonucleotides. Bennett does not add anything to Drayna that would make obvious the invention of the pending claims.

In fact, Applicants respectfully submit that an obviousness rejection based on a combination of Bennett and Drayna is defective for several reasons.

First, taking each reference as a whole, the combination of Bennett and Drayna does not provide any *suggestion* of the antisense sequences of claim 1. An obviousness rejection cannot be made by combining documents to make the bald suggestion that it is "obvious to try" to make antisense compounds to target CETP.

Second, in the above rejection, the examiner has selected only isolated components from the two references, ignoring other teachings of those same references. For example, only the generic teachings of Bennett with respect to antisense compounds are selected, without regard to the fact that Bennett was directed to a

completely different (both structurally and functionally) protein, PECAM-1. The rejection combines these selected components with Drayna's admitted ***speculations*** as to a use for CETP to purportedly make a *prima facie* case of obviousness of the claimed invention. It is wholly inconsistent with established patent law that only that portion of each cited document which supports the examiner's position is relied upon in the rejection, while the remaining teachings of the combined cited documents are ignored as if irrelevant. This type of construction of an obviousness rejection disregards the standard patent law that references must be taken as a whole, not in pieces.[1]

Third, the examiner would find no reason to have combined the teachings of Bennett with Drayna initially without the impermissible application of hindsight. The only motivation to perform such a combination of components is derived from Applicants' disclosure. The combination of these two prior art references to reject the pending claims of the present application is based simply on a prior reading of Applicants' invention. The examiner may not use Applicants' disclosure as a blueprint for piecing together prior art to defeat patentability in an improper manner. One of skill in the art would not have made this combination of elements, i.e., a description of the cloning of CETP combined with a disclosure relating to anti-sense

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1 *In re Oetiker*, 977 F2d 1443, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992) "There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the applicant's invention itself."

compounds that hybridize to PECAM-1, without the impermissible application of hindsight.[2] The examiner's reliance on hindsight is clearly improper. The mere fact that the prior art may be modified in the manner suggested by the examiner does not make the modification obvious, unless the prior art *suggested* the desirability of the modification. As discussed above, the prior art references in combination and taken as a whole do not suggest the claimed invention.

For the reasons set forth above, Applicants submit that this rejection may be properly withdrawn as against the pending claims.

B. The combination of Liu and Bennett does not make obvious the present invention.

Liu refers to the use of an ApoE peptide in a delivery complex with a ***single*** phosphoro-thioated antisense oligonucleotide (referred to as an AS-ODN) targeting nucleotides 329 to 349 of CETP cDNA and the delivery of the complex to a human CETP-transfected cell line. Of its results, Liu suggests

> "This ***approach may*** enable gene regulation *in vivo* and ***could possibly be used*** as an antiatherosclerotic agent to alter high density lipoprotein metabolism." (Emphasis added; Page 2207, abstract, last line); and

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[2] See, e.g., *In re Dembiczak*, 50 USPQ2d 1614, 1616-1617 (Fed. Cir. 1999): "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight. ..."

> The ***combined*** use of this peptide and AS-ODNs achieved the effective downregulation of CETP expression *in vitro*. (Emphasis added; Page 2208, col. 1)

As described by Liu, the CHO cells were transfected with one of the AS-ODN labeled with FITC alone, or the complex formed by the AS-ODN labeled with FITC and the ApoE peptide (AS-ODN/ dpGapoE) or with a similarly-labeled sense oligo/ApoE complex (S-ODN/dpGapoE). As can be clearly seen in Fig. 3B of Liu, the single antisense compound alone produced ***no decrease*** in CETP expression when compared to a control. Further, the authors themselves opine:

> "These results demonstrate that a human CETP AS-ODN complex with dpGapoE, ***but not naked AS-ODN***, suppressed CETP expression in hCETP CHO Cells *in vitro*. (Emphasis added; Page 2212, col. 2).

Further Liu states that since no similar inhibitory effect was noted with S-ODN,

> "[t]his result strongly supports the idea that inhibition of the CETP gene was ***sequence-specific***." (Emphasis added; Page 2212, col. 2).

The combination of the disclosure of Liu with that of Bennett fails to make obvious the claimed invention of Applicants.

Bennett, as discussed above, refers to antisense compounds useful to inhibit expression of PECAM-1, a completely different protein. Liu refers to a single antisense compound that binds a specific sequence of CETP and appears to inhibit expression thereof only in a complex with an apoE peptide. Liu does not teach that ***any*** AS-ODN to ***any*** region of CETP inhibits expression. In fact, the above-quoted remark would appear contrary to

that assumption. These references taken together do not teach or suggest the invention taught by the pending claims.

Applicants are not claiming "how to make" generic AS-ODN's, nor do they claim how to make Liu's specific AS-ODN to CETP. Applicants' claims are directed to novel AS-ODNs that are neither taught nor suggested by these references in combination. Bennett taken with Liu does not provide the required motivation for selection of particular CETP sequences recited in claim 1 ***for CETP***, nor any prediction of success with respect ***to CETP*** as the target. Bennett's teachings of AS-ODNs that target certain regions of PECAM-1, taken with Liu which refers to a single AS-ODN complexed with an apoE peptide, taken together, do not make obvious the presently claimed invention.

As discussed above with respect to the alternative obviousness rejection, these two documents cannot simply be cited to make the bald suggestion that it is "obvious to try" to make such antisense compounds to target CETP. "Obvious to try" is not a proper basis for an obviousness rejection. The combination of Bennett and Liu does not provide any *motivation* nor *expectation of success* that if one did target the ***specifically claimed*** sequences of the present claims, that one would obtain a desired inhibitory result. This is true when you consider that Bennett's teachings are directed to AS-ODN's to ***PECAM-1*** and Liu's representation is based upon a single AS-ODN to a different portion of the ***CETP*** sequence. This combination of art does not make obvious the presently claimed invention.

The only source of the required motivation to make and use antisense compounds directed to specific sequences of CETP recited in claim 1, which sequences are

not identified by either cited reference, is provided by the Applicants' own specification. The only teachings which supply the necessary motivation and expectation of success that such a composition would be useful are provided by the instant specification. Obtaining the motivation for combination of the prior art cannot properly be provided by Applicants' own disclosure. Applicants maintain that the combination of the cited prior art, when the teachings are taken *as a whole*, fails to supply both the motivation and a reasonable expectation of success required to set forth obviousness of the pending claims.

In view of the above amendments and these remarks, Applicants' respectfully request that the examiner withdraw the outstanding rejections and permit the above pending claims to pass to issue in due course.

The Director is hereby authorized to charge any additional fees required with the filing of this paper or credit any overpayment in any fees to our deposit account number 08-3040.

Respectfully submitted,

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